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[Lab. of Clinical Pharmaceutics]

### **Age-related Change of Plasma Extracellular-Superoxide Dismutase.**

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Extracellular-superoxide dismutase (EC-SOD) is a secretory protein that is the major SOD isozyme in extracellular fluids. Plasma EC-SOD mass concentrations in individuals were distributed in two discrete groups with the rare group (2.9%) having a variant of the enzyme with about 15-fold higher plasma levels. The EC-SOD level of the common phenotype in children/youths was significantly higher than that in their parents, and decreased with age, with an average decrease of about 2% per year to age 20. On the other hand, the parents' EC-SOD increased slightly with age. The cord EC-SOD level was the lowest. We observed no significant age-dependent changes in mass concentrations of Cu,Zn-SOD or Mn-SOD. Three SOD isozymes function together in a complementary manner as a consequence of different cellular and subcellular distributions. However, the results suggest that the changes in EC-SOD levels may be the most sensitive biomarker for age-related changes in the antioxidant capacity.

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[Lab. of Clinical Pharmaceutics]

### **Plasma Extracellular-Superoxide Dismutase in Healthy Newborns and Infants/Children.**

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The plasma level of EC-SOD might affect physiological and pathological conditions of the vascular system since this enzyme is the principal enzymatic scavenger of superoxide in the extracellular spaces and is present in the circulation in equilibrium between the plasma phase and the glycosaminoglycans of the endothelium. The aim of this study was to investigate the age-correlated changes of EC-SOD in early childhood. The EC-SOD levels reached its peak at about 1-year-old and then gradually decreased. There was a significant positive correlation between EC-SOD and age in the subgroup of infants below 1-year-old. However, a significant negative correlation was found in subgroup of those above 1-year-old. Maturation of the amounts and characteristics of glycosaminoglycans might contribute to the increase of the ability to bind to EC-SOD. The age-dependent decrease of EC-SOD above 1-year-old might be due to an increase in tissue binding ability of EC-SOD.

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[Lab. of Clinical Pharmaceutics]

### **Inhibitory Effect of Nitric Oxide on the Induction of Cytochrome P450 3A4 mRNA by 1,25-Dihydroxyvitamin D<sub>3</sub> in Caco-2 cells.**

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Nitric oxide (NO) released during inflammation is presumed to be involved in the down-regulation of many cytochrome P450 (CYP) genes. CYP3A4, which participates in the metabolism of various drugs, is known to be induced by 1,25 dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) in Caco-2. In this study, we examined whether NO affected CYP3A4 gene expression induced by 1,25(OH)<sub>2</sub>D<sub>3</sub> in Caco-2 cells. Induction of CYP3A4 mRNA by 1,25(OH)<sub>2</sub>D<sub>3</sub> was suppressed in a dose-dependent manner by treatment with the NO donors NOR-4 or SNAP. Treatment with the guanylate cyclase inhibitor ODQ failed to prevent the inhibition of induction of CYP3A4 mRNA by 1,25(OH)<sub>2</sub>D<sub>3</sub>. 8-Bromo cGMP had no effect on 1,25(OH)<sub>2</sub>D<sub>3</sub>-induced CYP3A4 gene expression. Therefore, the suppression of CYP3A4 mRNA by NO might be mediated through a guanylate cyclase-independent pathway.

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[Lab. of Clinical Pharmaceutics]

### **Effects of Homocysteine on the Binding of Extracellular-Superoxide Dismutase to the Endothelial Cell Surface.**

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Homocysteine is known to be a risk factor for several vascular diseases. Previously, we found a significant association between plasma homocysteine and plasma extracellular-superoxide dismutase (EC-SOD) levels. The binding of EC-SOD to human and bovine aortic endothelial cell cultures showed significant decreases after incubation with 10 μM homocysteine, whereas the expression of EC-SOD in fibroblast cell cultures was inhibited with a high concentration (1 mM) of homocysteine. Furthermore, binding of EC-SOD to heparin immobilized on plates was decreased with homocysteine. These observations suggested that homocysteine decreases the binding of EC-SOD to vascular endothelial cell surfaces by degradation of endothelial heparan sulfate proteoglycan, which results in a loss of the ability to protect endothelial cell surfaces from oxidative stress.